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10/087,602	03/01/2002	Matthew Patricelli	063391-0302	7925

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EXAMINER	
COUNTS, GARY W	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 01/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,602	PATRICELLI, MATTHEW	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-32 and 48-74* is/are pending in the application.

4a) Of the above claim(s) *60-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-32,48-59 and 74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

The amendment filed October 28, 2005 is acknowledged and has been entered.

Election/Restrictions

1. Applicant's election with traverse of Group I, Claims 21-32, 48-59 and 74 in the reply filed on October 28, 2005 is acknowledged. The traversal is on the ground(s) that a thorough search of Group II claims would, of necessity, involve a search of the subject matter of Group I claims. This is not found persuasive because restriction requirements are set forth for reasons of patentable distinction between each independent invention so as to warrant separate classification and search. The record set forth in the previous restriction requirement clearly indicated that the delineated inventions are in fact patentably distinct each from the other or independent from the other. Further, while searches would be expected to overlap, there is no reason to expect the searches to be coextensive.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 21-28, 30-32, 48-54, 56-59 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (US 2002/0076739) in view of Cravatt et al (US 2002/0045194).

Aebersold et al disclose affinity tagged reagents (chemical probe) for use in methods of determining target protein abundance between proteomes (complex protein mixtures). Aebersold et al discloses that these chemical probes bind to specific sites of target proteins (p. 2, paragraph 0017). Aebersold et al disclose contacting the complex protein mixture with the chemical probes (p. 7, col 1, lines 1-14). Aebersold et al disclose digesting the proteins in the sample mixture with proteolyzing agents (p. 7, paragraph 0070). Aebersold et al disclose separating the affinity tagged peptides by affinity isolation procedures (p. 7, paragraph 0071). Aebersold et al disclose analyzing the isolated-tagged peptides (those containing the probe) by liquid chromatography-mass spectrometry or capillary electrophoresis-mass spectrometry (p. 7, paragraph 0072). Aebersold et al disclose the removal of excess affinity tagged reagent (probe) prior to the step of digestion (p. 7, paragraph 0069). Aebersold et al disclose the use of internal standards in the method (p 6).

Aebersold et al differ from the instant invention in failing to teach the probe is an activity based probe and the use of a single activity based probe.

Cravatt et al disclose probes that have specificity to the active form of proteins (abstract). Cravatt et al disclose that these probes provides for methods for the measurement of specific active proteins in a proteome (p. 12, paragraphs 0116-0018). Cravatt et al disclose that the probe may contain a fluorescent moiety (p. 11, para. 0110). Cravatt et al disclose the use of antibodies to capture ligands comprising a fluorescent moiety (p. 9, paragraph 0095). Cravatt et al teach measurement of the active proteins in single and combined samples. Cravatt et al specifically teach that a single activity based probe can be used in the methods (p. 12, paragraph 0118). Cravatt et al disclose that these activity based probes provide for methods of measuring protein activity in proteomics, as opposed to protein abundance (paragraph 0005). Cravatt et al disclose that active target proteins such as enzymes are key to almost every biologic process and that current preteomic approaches are limited to abundance of active target proteins and that this is a key limitation because the activity of enzymes is often regulated by post-translational modification (paragraph 0005).

It would have been obvious to one of ordinary skill in the art to substitute the activity based probe such as taught by Cravatt et al for the probe of Aebersold et al because Cravatt et al teaches the use of a single probe in single and combined samples and also because Cravatt et al recognized the need for methods of measuring protein activity in proteomics, as opposed to protein abundance (taught by Aebersold et al). Further, Cravatt et al discloses that active target proteins such as enzymes are key to

almost every biologic process and that current preteomic approaches are limited to abundance of active target proteins and that this is a key limitation because the activity of enzymes is often regulated by post-translational modification. Therefore, a skilled artisan can have a reasonable expectation of success in incorporating an activity based probe taught by Cravatt et al in the method of Aebersold et al.

With respect to the recitation "specifically binds predominantly to a single target site" as recited in the instant claims. Cravatt et al disclose that the activity based probes are comprised of the formula R*(F-L)-X (para 0083) and discloses a list of ligands X which are used in the formula (para. 0095). This activity based probe is the same as the activity based probe disclosed by applicant on page 15, paragraph 0049 of the specification and contains the same ligands (see pages 16-17, paragraph 0055 of the specification). Therefore, the activity based probe of Cravatt et al would specifically bind predominantly to a single target site.

5. Claims 29 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al and Cravatt et al in view of Little et al (Us 2003/0003465).
See above for teachings of Aebersold et al and Cravatt et al.

Aebersold et al and Cravatt et al differ from the instant invention in failing to teach prior to the proteolyzing step, the one or more active target protein bound to the probe are bound to a solid support.

Little et al disclose immobilizing a target polypeptide (protein) to a solid support. Little et al disclose that the target polypeptide (protein) can be immobilized by a streptavidin or avidin to biotin interactions (p. 9, paragraph 073). Little et al disclose that

the immobilization of a target polypeptide (protein) provides a means to isolate the polypeptide, as well as a means to manipulate the isolated target polypetide prior to mass spectrometry (p. 3, lines 1-6). Little et al disclose that the term polypeptide and protein are interchangeable (p. 5, paragraph 0045).

It would have been obvious to one of ordinary skill in the art to immobilize the active target protein complex of Aebersold and Cravatt et al to a solid support prior to the proteolysing step because Little et al teaches that the immobilization of a target polypeptide (protein) provides a means to isolate the polypeptide, as well as a means to manipulate the isolated target polypetide prior to mass spectrometry. Further, Aebersold et al teaches isolating the bound complex from excess probe prior to the proteolyzing step. Therefore a skilled artisan would have a reasonable expectation of success immobilizing the active target protein complex prior to a proteolyzing step.

Response to Arguments

6. Applicant's arguments filed October 28, 2005 have been fully considered but they are not persuasive.

Applicant argues that the Examiner asserts that the combination of Cravatt and Aebersold teach all of the elements of the invention as claimed, curing the defects of the application of the Aebersold reference by itself because Cravatt "teaches the analysis of a single sample". However, the Examiner's assertion is not accurate. Applicant states that Cravatt does not contemplate a method for analyzing proteins in a single complex protein mixture, e.g. a proteome, herein each element of the present invention, as required from example in claim 21, is described. Applicant states that when a single

activity based probe is used to label a protein sample, protein digestion is done after separation. See Cravatt paragraphs [0107] and [0183-0184]. Cravatt only contemplates protein digestion prior to separation when two or more protein samples are quantitatively compared using sets of isotopically labeled acitivity based probes. Applicant directs Examiner's attention of paragraph [0128] of Cravatt. This is not found persuasive because Examiner has not relied upon Cravatt for teaching these steps but rather has relied upon Aebersold et al for teaching protein digestion and subsequent separation. As indicated above and in the previous office action Cravatt et al is relied upon for teaching the probe is an activity based probe and the use of a single activity based probe. Further, as indicated above and in the previous office action it would have been obvious to substitute the activity based probe of Cravatt et al for the probe of Aebersold et al. Thus, the combined references teach the steps as disclosed by Aebersold et al using a probe such as taught by Cravatt. Further, it appears that applicant is relying on the recitation in the claims in which a single activity based probe that specifically binds predominantly to a single target site on the one or more active target proteins is used. However, the "consisting essentially of" as recited in claim 21 and the comprising language used in claims 49 and 74 would include the inclusion of other components. Unless there is a recitation in the claims which excludes other components, the claims as recited encompasses the teachings of Aebersold et al and Cravatt et at. With respect to the "consisting essentially of" as recited in the instant claims for the purposes of searching for and applying prior art under 102 & 103, absent a clear indication in the specification or claims of what the basic novel characteristics

actually are, "consisting essentially of" will be construed as equivalent to "comprising". Therefore, the method as recited can include other probes and absent evidence to the contrary the addition probes would not materially affect the basic and novel characteristic of the claimed invention (See MPEP 2111.03).

Applicant argues that contrary to the Examiner's assertion, recognition of a need in the art is not the same as an expectation of success. Mere recognition of a need may provide the motivation to try, but it clearly does not, without more, rise to the level of an expectation of success. Applicant states that the Examiner has provided absolutely no support from either Aebersold or Cravatt for the assertion that a skilled artisan would have an expectation of success in the combination of the Cravatt and Aebersold methods. This is not found persuasive because both Aebersold et al and Cravatt et al disclose determining proteins in a sample by using affinity probes and Cravatt et al specifically teaches these probes provide advantages over known probes in the art of protein detection. Thus, one of ordinary skill in the art would have a reasonable expectation of success. Further, it is unclear why one of ordinary skill in the art would not have a reasonable expectation of success. Applicant has not provided any evidence that one of ordinary skill would not have a reasonable expectation of success.

Applicant disagrees with the Examiner's assertion that "applicant is arguing the references individually." (See page 9, lines 2-3 of the Office Action). Applicant states that before one can consider the potential impact of a combination of references, one must look at the teaching of each reference individually. Examiner agrees that one must look at references individually. However, the rejections are based on the

combination of the references and one cannot argue that individual references fail to meet the limitations of the claims. The motivation to combine Aebersold and Cravatt is clearly laid out and the combination of references meet the limitations of the claims

Applicant argues that labeling with the acitivity based probes of the present invention's methods produce fewer peptides than the use of the Aebersold probes. Once again, the rejection is not based on Aebersold probes but rather is made from the combination of Aebersold et al and Cravatt et al. Applicant states that the reason fewer peptides are produced by the present method is not because the present invention employs a single activity based probe and Aebersold employs multiple probes, Instead, fewer peptides are produced because activity based probes, as defined in the present invention, react with a specific amino acid side chain only when it is within a particular structural/function context, i.e. an enzyme active site. This is not found persuasive because In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., acitivity based probes react with a specific amino acid side chain only when it is within a particular structural/functional context, i.e., an enzyme activity site) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Applicant further states that in contrast the Aebersold probes, when similarly applied, will label each individual serine residue present. This is not found persuasive because Applicant is arguing Aebersold individually. The current rejection is based on the combination of Aebersold

et al and Cravatt et al and as stated above and in the previous office action Cravatt et al disclose that the activity based probes are comprised of the formula R*(F-L)-X (para 0083) and discloses a list of ligands X which are used in the formula (para. 0095). This activity based probe is the same as the activity based probe disclosed by applicant on page 15, paragraph 0049 of the specification and contains the same ligands (see pages 16-17, paragraph 0055 of the specification). Therefore, the probe of Cravatt would possess the same binding capabilities as the probe recited and the combination of Aebersold et al and Cravatt would have the same steps using the same probe as instantly recited and would therefore would produce fewer peptides and the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya,* 227, USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant argues that differences between the use of single activity based probes and sets of isotopically labeled probes are very significant. Once again it appears that applicant is relying on the recitation in the claims in which a single activity based probe that specifically binds predominantly to a single target site on the one or more active target proteins is used. However, the "consisting essentially of" as recited in claim 21 and the comprising language used in claims 49 and 74 would include the inclusion of other components. Unless there is a recitation in the claims which excludes other components, the claims as recited encompasses the teachings of Aebersold et al and Cravatt et at. With respect to the "consisting essentially of" as recited in the instant

claims for the purposes of searching for and applying prior art under 102 & 103, absent a clear indication in the specification or claims of what the basic novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising". Therefore, the method as recited can include other probes and absent evidence to the contrary the addition probes would not materially affect the basic and novel characteristic of the claimed invention (See MPEP 2111.03).

Applicant further states that activity based probes label a single target site on each protein, resulting in a single labeled peptide from each protein after digestion, In contrast Aebersold probes label multiple sites on each protein, resulting in an increased number of peptides. Prior to the present invention, the standard belief in the mass spectrometry community was that a single peptide did not provide data with sufficient confidence to unambiguously identify a protein through automated sequence searching. This is not found persuasive because the motivation to combine the references comes from the teachings as stated above because Cravatt et al teaches the use of a single probe in single and combined samples and also because Cravatt et al recognized the need for methods of measuring protein activity in proteomics, as opposed to protein abundance (taught by Aebersold et al). Further, Cravatt et al discloses that active target proteins such as enzymes are key to almost every biologic process and that current preteomic approaches are limited to abundance of active target proteins and that this is a key limitation because the activity of enzymes is often regulated by post-translational modification. Further, as stated by Applicant on page 18 of the Remarks section filed April 26, 2005. The activity based probes of the present invention (which

are the same probes as Cravatt (see above rejections)) are larger than the Aebersold probes and the labeling sites of the probes result in very large peptides allowing for mass spectrometry data. Therefore, one of ordinary skill in the art would expect the combination of Aebersold and Cravatt to provide data to identify a protein. With respect to the remaining arguments directed to the Aebersold probe on pages 15-17, Applicant is arguing the characteristics of the Aebersold probe and not arguing the combination of Aebersold et al and Cravatt et al, in which the activity based probe of Cravatt et al is used in the method of Aebersold et al and thus it appears that Applicant is arguing the reference individually and not arguing the combination of Aebersold et al and Cravatt et al and as stated above it is the Examiner's position that motivation to combine the two references is clearly provided and that the combination of the two references reads on the instantly recited claims for reasons stated above and in the previous office actions.

Applicant argues that Little is unable to cure the deficiencies of Aebersold or Cravatt, taken alone or in combination, as Little addresses none of the acknowledged limitations of Aebersold or Cravatt, taken alone or in combination. This is not found persuasive because it is the Examiner's position that the combination of Aebersold and Cravatt is appropriate and reads on the instantly recited claims and also, that the combination of Little with Aebersold and Cravatt is appropriate and reads on the instantly recited claims.

Conclusion

7. No claims are allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary Courts
Examiner
Art Unit 1641
January 9, 2006

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01/16/06